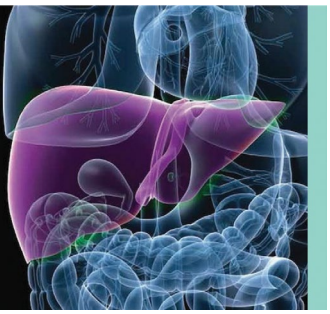

Ascites After Liver Transplantation

Michelle Jenkins, M.S.H.S., PA.-C., and Rohit Satoskar, M.D., F.A.A.S.L.D.

Ascites is a clinical complication of cirrhosis that occurs due to hemodynamic changes that result in circulatory malfunction, causing systemic and splenic vasodilation as a result of increased nitric oxide.[1] The presence of persistent ascites pretransplant is associated with poor survival, and thus these patients are best served by transplant.[2] Following orthotopic liver transplant (OLT), ascites is expected to resolve within 2 to 4 weeks as reversal of previous systemic derangements occurs.[1,3] Persistent ascites, defined as ascites more than 4 weeks after successful OLT, is a rare occurrence but has been described to occur in 3% to 7% of patients.[1-5] Patients with persistent ascites after transplant have increased morbidity and decreased 1-year survival.[3-5]

ETIOLOGY AND RISK FACTORS

Causes of posttransplant ascites, as shown in Fig. 1, include alterations in hepatic inflow, outflow obstruction, rejection (both acute and chronic), recurrent hepatitis, infection, renal dysfunction, and heart failure.[1-5]

Hepatic outflow obstruction results in postsinusoidal portal hypertension (HTN) and is perhaps the most common causative factor in patients with persistent ascites posttransplantation. Outflow obstruction following OLT is caused by stenosis of the caval anastomosis and can occur regardless of the surgical technique used, piggyback or caval anastomosis.[1-3] Hepatic inflow obstruction posttransplant is rare but often occurs in the setting of portal vein thrombosis (PVT). The cause of PVT is thought to be related to vessel reconstruction, with higher incidence in patients with prior PVT history.[6] This contrasts with pretransplant PVT, which uncommonly results in ascites. In patients with severe portal HTN prior to transplant, persistent increased portal inflow after transplantation may also contribute to the development of ascites.[7]

Acute cellular rejection (ACR) after transplant is not very well studied as a cause of posttransplant ascites, but some evidence suggests that it may contribute to ascites development as a result of decreased compliance of the hepatic vasculature.[4] In one study, patients with ACR had a higher hepatic venous pressure gradient (HVPG) than those without, and HVPG increased proportionately with the severity of rejection.[8] Ascites typically resolved after the ACR episode was treated unless chronic rejection developed.

Abbreviations: ACR, acute cellular rejection; CIT, cold ischemic time; DAA, direct-acting antiviral; HCV, hepatitis C virus; HTN, hypertension; HVPG, hepatic venous pressure gradient; OLT, orthotopic liver transplant; PVT, portal vein thrombosis; SAE, splenic artery embolization; TIPS, transjugular intrahepatic portosystemic shunt.

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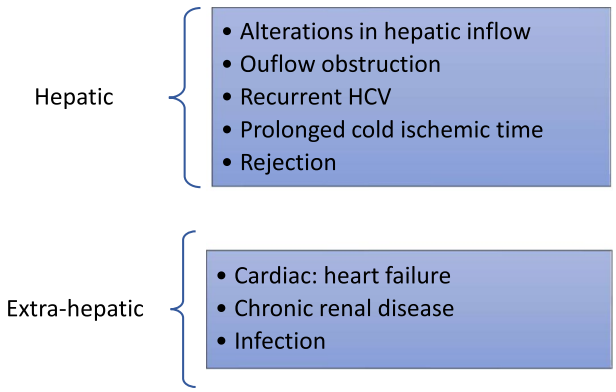

FIG 1 Causes of posttransplant ascites.

Some studies have shown that patient risk factors, such as sex, presence of hepatitis C virus (HCV), and cold ischemic time (CIT), may also predispose patients to ascites development. Males may be at greater risk for ascites development, but the data regarding this are limited.[1,4] Prior to the widespread use of direct-acting antivirals (DAAs), patients who had transplant for HCV-related disease were at higher risk for persistent ascites. HCV recurrence after liver transplantation can result in ascites even in the absence of significant fibrosis. According to two retrospective studies, ascites was found in patients with stage 0, 1, or 2 fibrosis on allograft biopsy.[5,9] Positive cryoglobulinemia in HCV-positive patients was also found to be predictive of ascites development.[9] There are limited data on ascites resolution after HCV treatment, particularly with use of DAAs. However, in our experience, ascites generally resolves after HCV treatment if advanced fibrosis is not present. Prolonged CIT is thought to result in ischemic injury of sinusoidal endothelial cells that can cause inadequate accommodation of blood flow.[1,4,10] Extended CIT damages the endothelium of the sinusoids, causing decreased production of nitric oxide, resulting in increased vasoconstriction leading to increased portal pressure and flow.[5,11] Additional risk factors that have not been well studied include reduced size graft and older donors.

EVALUATION

Figure 2 shows a workup of posttransplant ascites. Diagnostic paracentesis should be performed to evaluate for infection and determine the character of the ascitic fluid. Serum to ascites albumin gradient may help determine whether portal HTN is a cause, but in our experience is not as reliable as in the pretransplant setting. After diagnostic paracentesis, imaging with ultrasound liver Doppler and/or

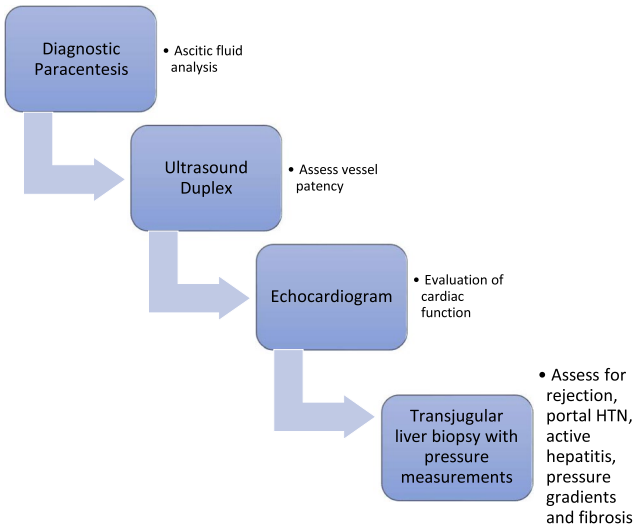

FIG 2 Diagnostic workup of posttransplant ascites.

contrast-enhanced cross-sectional imaging to evaluate vessel patency should be performed. Transthoracic echocardiogram should also be obtained to evaluate for evidence of cardiac dysfunction. Finally, transjugular liver biopsy with pressure measurements and venogram may ultimately be needed to evaluate for pressure gradients, portal HTN, and the presence of active hepatitis or fibrosis.

TREATMENT

Treatment of ascites after liver transplant is directed toward the underlying cause, if modifiable. Patients with outflow obstruction can undergo balloon angioplasty or surgical repair, and this often results in prompt resolution of ascites. In patients without a modifiable cause, diuretics are used. Unfortunately, renal impairment or electrolyte disturbances can develop that require treatment with therapeutic paracentesis.

Transjugular intrahepatic portosystemic shunts (TIPSs), typically used as a bridge to transplant for patients with cirrhosis, have also been used for ascites management posttransplant. There has been controversy regarding the technical difficulty of TIPS placement in a transplanted liver versus a native liver; however, a retrospective study found no statistical significance regarding the success rates.[12] Complications of TIPS placement in a liver transplant recipient includes risk for puncture of the liver capsule, infection, TIPS dysfunction, decline in liver function, infection, and hepatic encephalopathy.[12,13] There is wide variation of clinical success with TIPS following OLT that is described to

be between 16% and 58%, which is lower than in the pretransplant population, and graft survival 6 to 12 months after TIPS is 45% to 50%.[13] Given the varying success, many patients may continue to warrant therapeutic paracentesis after TIPS placement or may require TIPS revision.

In recent years, the use of splenic artery embolization (SAE) has been performed as an alternative to TIPS and has been shown to be effective in decreasing portal hyperperfusion by reducing portal vein flow, and therefore portal pressure and hepatic congestion.[13,14] Previously used primarily for patients undergoing living donor liver transplant, it has now been shown to also be effective in the management of ascites. Complications related to SAE include postembolization syndrome, reported to occur in ~78% of patients,[15] splenic abscess, splenic infarct, pancreatitis, and splenic rupture. In addition, it has been reported that the rate of complication increases based on the placement of the coils, with distal placement increasing the risk for complication.[13] The success of the SAE is measured by reduction in weight, resolution of ascites on imaging, and decrease in portal vein velocity as measured by the spleen/liver volume ratio.[13-16] Patients with low spleen/liver volume ratios (<0.5) before SAE showed decreased response to SAE with persistence of ascites; thus, SAE works best when spleen/liver volume ratios are >0.5[13-16] Ongoing studies of SAE continue to show high rates of clinical success and minimal complications.[13-16]

In conclusion, the occurrence of ascites posttransplant is uncommon but can result in increased morbidity and mortality. Causes include technical issues related to the transplant surgery, patient- and/or donor-related factors, including, but not limited to, outflow obstruction, recurrent HCV, and prolonged CIT. Evaluation of posttransplant ascites requires a stepwise approach to guide management and treatment. For patients without a defined modifiable cause, the initial step in treatment is often the use of diuretics; however, use is often limited by underlying renal dysfunction, as well as electrolyte disturbances. In patients who do not respond successfully to conservative treatment, TIPS is often considered; however, TIPS can have variable efficacy and has risk for complications. SAE is emerging as a safe and more effective alternative to TIPS placement in reduction of portal inflow and has resulted in resolution of ascites.

CORRESPONDENCE

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REFERENCES

1) Stewart CA, Wertheim J, Olthoff K, et al. Ascites after liver transplantation—a mystery. Liver Transpl 2004;10:654-660.

2) Nishida S, Gaynor JJ, Nakamura N, et al. Refractory ascites after liver transplantation: an analysis of 1058 liver transplant patients at a single center. Am J Transplant 2006;6:140-149.

3) Gotthardt DN, Weiss KH, Rathenberg V, et al. Persistent ascites after liver transplantation: etiology, treatment and impact on survival. Ann Transplant 2013;18:378-383.

4) Cirera I, Navasa M, Rimola A, et al. Ascites after liver transplantation. Liver Transpl 2000;6:157-162.

5) Lan BY, Landry GM, Tan VO, et al. Ascites in hepatitis C liver transplant recipients frequently occurs in the absence of advanced fibrosis. Am J Transpl 2008;8:366-376.

6) Bonnel AR, Bunchorntavakul C, Reddy KR. Transjugular intrahepatic portosystemic shunts in liver transplant recipients. Liver Transpl 2014;20:130-139.

7) Hadengue A, Lebrec D, Moreau R, et al. Persistence of systemic and splanchnic hyperkinetic circulation in liver transplant patients. Hepatology 1993;17:175-178.

8) Gadano A, Hadengue A, Widmann JJ, et al. Hemodynamics after orthotopic liver transplantation: study of associated factors and long-term effects. Hepatology 1995;22:458-465.

9) Tripon S, Francoz C, Albuquerque A, et al. Interactions between virus-related factors and post-transplant ascites in patients with hepatitis C and no cirrhosis: role of cryoglobulinemia. Transplant Int 2015;28:162-169.

10) Ohkohchi N. Mechanisms of preservation and ischemic/reperfusion injury in liver transplantation. Transplant Proc 2002;34:2670-2673.

11) Iwakiri Y. Endothelial dysfunction in the regulation of cirrhosis and portal hypertension. Liver Int 2012;32:199-213.

12) Saad WE, Darwish WM, Davies MG, et al. Transjugular intrahepatic portosystemic shunts in liver transplant recipients: technical analysis and clinical outcome. AJR Am J Roentgenol 2013;200:210-218.

13) Quintini C, D'Amico G, Brown C, et al. Splenic artery embolization for the treatment of refractory ascites after liver transplantation. Liver Transpl 2011;17:668-673.

14) Meighani A, Jafri SMR, Raoufi M, et al. Splenic artery embolization for treatment of refractory ascites after liver transplantation. ACG Case Rep J 2016;3:136-138.

15) Chang CY, Singal AK, Ganeshan SV, et al. Use of splenic artery embolization to relieve tense ascites following liver transplantation in a patient with paroxysmal nocturnal hemoglobinuria. Liver Transpl 2007;13:1532-1537.

16) Presser N, Quintini C, Tom C, et al. Safety and efficacy of splenic artery embolization for portal hyperperfusion in liver transplant recipients: a 5-year experience. Liver Transpl 2015;21:435-441.